

E. Chloroprene PBPK Model Equations

#Chloroprene PBPK Model

#Translated into R from the acslX model presented in Yang et al. 2012

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#The full model code, including the scripts for running the model, is available from the authors.

```
States = {
```

```
AI ,
```

```
AX ,
```

```
AM ,
```

```
AMLU ,
```

```
AMK ,
```

```
ALU ,
```

```
AL ,
```

```
AK ,
```

```
AS ,
```

```
AR ,
```

```
AF
```

```
};
```

```
Outputs = {
```

```
MASBAL ,
```

```
CLU ,
```

```
CL ,
```

```
CK ,
```

```
CS ,
```

```
CR ,
```

```
CF ,
```

```
CVLUM ,
```

```
ppm ,
```

```
AMP ,
```

```
AMPLU ,
```

```
AMPK ,
```

```
cvl ,
```

```
qcbal ,
```

```
vbal
```

```
};
```

```
Inputs = {EXPPULSE};
```

```
#BODY WEIGHT (kg)
```

```
  BW = 0.03 ; # Body weight (kg)
```

#SPECIAL FLOW RATES

QPC = 29.1 ; # Unscaled Alveolar Vent (L/h/kg^{0.75})
QCC = 20.1 ; # Unscaled Cardiac Output (L/h/kg^{0.75})

#FRACTIONAL BLOOD FLOWS TO TISSUES

QLC = 0.161 ; # Flow to Liver as % Cardiac Output (unitless)
QFC = 0.07 ; # Flow to Fat as % Cardiac Output (unitless)
QSC = 0.159 ; # Flow to Slow as % Cardiac Output (unitless)
QKC = 0.09 ; # Flow to Kidney as % Cardiac Output (unitless)

#FRACTIONAL VOLUMES OF TISSUES

VLC = 0.055 ; # Volume Liver as % Body Weight (unitless)
VLUC = 0.0073 ; # Volume Lung as % Body Weight (unitless)
VFC = 0.1 ; # Volume Fat as % Body Weight (unitless)
VRC = 0.08098 ; # Volume Rapid Perfused as % Body Weight (unitless)
VSC = 0.384 ; # Volume Slow Perfused as % Body Weight (unitless)
VKC = 0.0167 ; # Volume Kidney as % Body Weight (unitless)

#PARTITION COEFFICIENTS PARENT

PL = 1.26 ; # Liver/Blood Partition Coefficient (unitless)
PLU = 2.38 ; # Lung/Blood Partition Coefficient (unitless)
PF = 17.35 ; # Fat/Blood Partition Coefficient (unitless)
PS = 0.59 ; # Slow/Blood Partition Coefficient (unitless)
PR = 1.76 ; # Rapid/Blood Partition Coefficient (unitless)
PB = 7.83 ; # Blood/Air Partition Coefficient (unitless)
PK = 1.76 ; # Kidney/Blood Partition Coefficient (unitless)

#KINETIC CONSTANTS

MW = 88.5 ; # Molecular weight (g/mol)

Metabolism in Liver

VMAXC = 7.95 ; # Scaled VMax for Oxidative Pathway:Liver (mg/h/BW^{0.75})
KM = 0.041 ; # Km for Oxidative Pathway:Liver (mg/L)

Metabolism in Lung

VMAXCLU = 0.18 ; # Scaled VMax for Oxidative Pathway:Lung (mg/h/BW^{0.75})
KMLU = 0.26 ; # Km for Oxidative Pathway:Lung (mg/L)
KFLUC = 0.0 ; # Pseudo-first order clearance in lung (Km unidentifiable) (L/hr/BW^{0.75})

Metabolism in Kidney

VMAXCKid = 0.0 ; # Scaled VMax for Oxidative Pathway:Kidney (mg/h/BW^{0.75})
KMKD = 0.0 ; # Km for Oxidative Pathway :Kidney
KFKIC = 0.079 ; # Pseudo-first order clearance in kidney (Km unidentifiable) (L/hr/BW^{0.75})

#DOSING INFORMATION

TSTOP = 7.0 ; # Dosing stop time
CONC = 13.0 ; # Initial concentration (ppm)

Dynamics {

Scaled parameters

QC = QCC*pow(BW,0.75) ; #Cardiac output
QP = QPC*pow(BW,0.75) ; #Alveolar ventilation
QL = QLC*QC ; #Liver blood flow
QF = QFC*QC ; #Fat blood flow
QS = QSC*QC ; #Slowly-perfused tissue blood flow
QK = QKC*QC ; #Kidney tissue blood flow
QRC = 1-QLC-QKC-QFC-QSC ; #Rapidly Perfused tissues
QR = QRC*QC ; #Rapidly-perf tissue blood flow

VL = VLC*BW ; #Liver volume
VLU = VLUC*BW ; #Lung volume
VF = VFC*BW ; #Fat tissue volume
VS = VSC*BW ; #Slowly-perfused tissue volume
VR = VRC*BW ; #Richly-perfused tissue volume
VK = VKC*BW ; #kidney tissue volume

ROBC = 1 - VLC - VLUC - VFC - VSC - VRC - VKC ; #Rest of body un-perfused tissue for MC sims

METABOLISM

VMAX = VMAXC*pow(BW,0.75) ; #Maximum rate of metabolism-Liver (mg/hr/kg-BW)
VMAXLU = VMAXCLU*pow(BW,0.75) ; #Maximum rate of metabolism-Lung (mg/hr/kg-BW)
KFLU = KFLUC*BW ;
VMAXKD = VMAXCKid*pow(BW,0.75) ; #Maximum rate of metabolism-Kidney (mg/hr/kg-BW)
KFKI = KFKIC*BW ;

Exposure Control (mg/L)

CIX = CONC*MW/24450 ;
CI = CIX *EXPPULSE ;

Tissue Venous Concentrations (mg/L)

CVLU = ALU/(VLU*PLU) ;
CVL = AL/(VL*PL) ;
CVK = AK/(VK*PK) ;
CVS = AS/(VS*PS) ;
CVR = AR/(VR*PR) ;
CVF = AF/(VF*PF) ;

Concentration in Pulmonary/Arterial and venous blood Compartments (mg/L)

$$\text{CPU} = (\text{QP} \cdot \text{CI} + (\text{QF} \cdot \text{CVF} + \text{QL} \cdot \text{CVL} + \text{QS} \cdot \text{CVS} + \text{QR} \cdot \text{CVR} + \text{QK} \cdot \text{CVK})) / (\text{QP} / \text{PB} + \text{QC}) ;$$

$$\text{CX} = \text{CPU} / \text{PB} ;$$

$$\text{CV} = (\text{QF} \cdot \text{CVF} + \text{QL} \cdot \text{CVL} + \text{QS} \cdot \text{CVS} + \text{QR} \cdot \text{CVR} + \text{QK} \cdot \text{CVK}) / \text{QC} ;$$

$$\text{CPUM} = \text{CPU} \cdot 1000 / \text{MW} ;$$

$$\text{RAI} = \text{QP} \cdot \text{CI} ;$$

$$\text{dt}(\text{AI}) = \text{RAI} ;$$

$$\text{RAX} = \text{QP} \cdot \text{CX} ;$$

$$\text{dt}(\text{AX}) = \text{RAX} ;$$

Amount metabolized in Liver (mg)

$$\text{RAM} = \text{VMAX} \cdot \text{CVL} / (\text{KM} + \text{CVL}) ;$$

$$\text{dt}(\text{AM}) = \text{RAM} ;$$

Amount metabolized in Lung (mg)

$$\text{RAMLU} = \text{VMAXLU} \cdot \text{CVLU} / (\text{KMLU} + \text{CVLU}) + \text{KFLU} \cdot \text{CVLU} ;$$

$$\text{dt}(\text{AMLU}) = \text{RAMLU} ;$$

Amount metabolized in Kidney (mg)

$$\text{RAMK} = \text{VMAXKD} \cdot \text{CVK} / (\text{KMKD} + \text{CVK}) + \text{KFKI} \cdot \text{CVK} ;$$

$$\text{dt}(\text{AMK}) = \text{RAMK} ;$$

Amount in Lung Compartment (mg)

$$\text{RALU} = \text{QC} \cdot (\text{CPU} - \text{CVLU}) - \text{RAMLU} ;$$

$$\text{dt}(\text{ALU}) = \text{RALU} ;$$

Amount in Liver Compartment (mg)

$$\text{RAL} = \text{QL} \cdot (\text{CVLU} - \text{CVL}) - \text{RAM} ;$$

$$\text{dt}(\text{AL}) = \text{RAL} ;$$

Amount in Kidney Compartment (mg)

$$\text{RAK} = \text{QK} \cdot (\text{CVLU} - \text{CVK}) - \text{RAMK} ;$$

$$\text{dt}(\text{AK}) = \text{RAK} ;$$

Amount in Slowly Perfused Tissues (mg)

$$\text{RAS} = \text{QS} \cdot (\text{CVLU} - \text{CVS}) ;$$

$$\text{dt}(\text{AS}) = \text{RAS} ;$$

Amount in Rapidly Perfused Tissues (mg)

$$\text{RAR} = \text{QR} \cdot (\text{CVLU} - \text{CVR}) ;$$

$$\text{dt}(\text{AR}) = \text{RAR} ;$$

Amount in Fat Compartment (mg)

RAF = QF*(CVLU - CVF) ;
dt(AF) = RAF ;

}# End of Dynamics

CalcOutputs {

Mass-balance

MASBAL = AI - AX - (AL+AM+AMLU+ALU+AK+AMK+AS+AR+AF) ;

#Tissue Concentrations (mg/L)

CLU = ALU/VLU ;

CL = AL/VL ;

CK = AK/VK ;

CS = AS/VS ;

CR = AR/VR ;

CF = AF/VF ;

#Concentrations for plots

CVLUM = CVLU*1000/MW ; #(umol/L)

#Dose metrics

ppm = CONC ;

AMP = ((AM*1000/MW)/(VL*1000))/(TSTOP/24) ;

AMPLU = ((AMLU*1000/MW)/(VLU*1000))/(TSTOP/24) ;

AMPK = ((AMK*1000/MW)/(VK*1000))/(TSTOP/24) ;

cvl = CVL ;

#Blood Flow balance

qcbal = QC - QL - QF - QS - QK - QR ;

#Tissue Volume balance

vbal = BW*(1-ROBC) - VL - VLU - VF - VS - VK - VR ;

}# End of CalcOutputs

End